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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/458,014	12/10/1999	JACQUES DUMAS	BAYER11-C1	8328

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EXAMINER
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CHONG, YONG SOO

ART UNIT	PAPER NUMBER
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1617

MAIL DATE	DELIVERY MODE
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01/15/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/458,014	<b>Applicant(s)</b> DUMAS ET AL.	
	<b>Examiner</b> Yong S. Chong	<b>Art Unit</b> 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 29 October 2007.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-34 and 37-58 is/are pending in the application.
- 4a) Of the above claim(s) 5-27, 37, 39-41, 52, 53 and 56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4 (in part), 28-34 (in part), 38, 42-51 (in part), 54-55 (in part), 57 (in part), 58 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some    \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

## **DETAILED ACTION**

### ***Status of the Application***

This Office Action is in response to applicant's arguments filed on 10/29/2007. Claim(s) 35-36 have been cancelled. Claim(s) 58 been added. Claim(s) 1-34, 37-58 are pending. Claim(s) 5-27, 37, 39-41, 52-53, 56 have been withdrawn. Claim(s) 1-4 (in part), 28-34 (in part), 38, 42-51 (in part), 54-55 (in part), 57 (in part), 58 are examined herein.

Applicant's arguments have been fully considered but found not persuasive. The rejection(s) of the last Office Action are maintained for reasons of record and modified below as a result of Applicant's claim amendments.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 (in part), 28-34 (in part), 38, 42-51 (in part), 54-55 (in part), 57 (in part), 58 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a method for the treatment of a disease mediated by p38 other than cancer comprising administering a compound of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the breadth of the claims; (4) the amount of direction or guidance presented; (5) the predictability or unpredictability of the art; (6) the relative skill of those in the art; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1) The Nature of the Invention: The rejected claims are drawn to an invention which pertains to a method for the treatment of a disease mediated by p38 other than cancer comprising administering a compound of formula I.

(2) State of the Prior Art: The state of the art regarding p38 inhibition has shown to inhibit both cytokine production (TNF $\alpha$ , IL-1, IL-6, IL-8) and proteolytic enzyme production (MMP-1, MMP-3). Clinical studies have linked TNF $\alpha$  production to a number of inflammatory and/or immunomodulatory diseases. There is no indication that such a link actually translates to treatment of the disease. Therefore, the same argument can be applied to p38 inhibition.

(3) Breadth of Claims: The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass virtually every disease or disorder that is mediated by p38 kinase. Furthermore, p38 kinase is

disclosed to inhibit both cytokine production (TNF $\alpha$ , IL-1, IL-6, IL-8) and proteolytic enzyme production (MMP-1, MMP-3). Therefore, the invention is complex because it involves any disease or disorder related to these cytokines or enzymes as being within the scope of this invention.

(4) Guidance of the Specification: The guidance of the specification discloses a pathway between inhibition of p38 and various inflammatory and/or immunomodulatory diseases through cytokine production (TNF $\alpha$ , IL-1, IL-6, IL-8) and proteolytic enzyme production (MMP-1, MMP-3). The specification does not disclose how to determine whether a disease or disorder can be treated by p38 inhibition, it only discloses that the two are linked together. As a result, one of ordinary skill in the art would be forced to perform an exhaustive search for the embodiments of any drug having the function recited in the instant claims suitable to practice the invention. Furthermore, one of ordinary skill in the art would have to determine not only which compounds inhibit p38, but which compounds are therapeutically effective on a p38 mediated disease. The specification shows examples of *in vitro* p38 inhibition but does not provide any raw data or what specific compounds were tested. The *in vivo* study was not performed on subjects with any diseases or disorders.

(5) The Predictability or Unpredictability of the Art: The invention is directed to a method for the treatment of a disease mediated by p38 other than cancer comprising administering a compound of formula I. Treatment of a disease involves many biochemical pathways mediated by many different proteins. It is not possible to predict the efficacy in the treatment of a disease simply by inhibition of p38.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutical effects, side effects, and especially serious toxicity that may be generated by drug-drug inerteractions when and/or after adminstering to a host (e.g., a human) any compound represented by formula I. See "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9<sup>th</sup> ed., 1996), page 51 in particular. *Goodman & Gilman* teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right of page 51) (emphasis added). In the instant case, in the absence of fully recognizing the identity of the member genus herein, one of skill in the art would not be able to fully predict possible adverse drug-drug interactions occurring with many combinations of any compounds having the claimed functional properties in the pharaceutical compositions herein. Thus, the teachings of *Goodman & Gilman* clearly support that the instant claimed invention is highly unpredictable.

(6) The Relative Skill of those in the Art: One of ordinary skill in the art knows how to inhibit p38 and how to effectively treat various inflammatory and/or immunomodulatory diseases, but does not know how to treat diseases that are not inflammatory or immunomodulatory by nature by inhibiting p38.

(7) Working Examples: The specification lacks any working examples of treating a p38 mediated disease comprising administering a compound of formula I. The only examples are drawn to an *in vitro* p38 kinase inhibition assay and *in vivo* inhibition of TNF $\alpha$  in mice. Examiner notes that there is no raw data for any of the disclosed compounds for either of these examples. Moreover, the mice are not disclosed to have a p38 mediated disease or disorder, therefore no disease is being treated in the examples.

(8) The Quantity of Experimentation Necessary: The specification fails to provide support for a method for the treatment of a disease mediated by p38 other than cancer comprising administering a compound of formula I. A large quantity of experimentation would be needed in order to discover what diseases or disorders can be treated by inhibition of p38 and to what extent. Nor does it provide information to practice the claimed invention, absent undue experimentation. *Genetech*, 108 F. 3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

### ***Response to Arguments***

Applicants maintain that the restriction requirement should be withdrawn in that all claims were previously examined and allowed on September 5, 2002. Applicant's direct Examiner's attention to the new rules FAQ to show that a restriction at this late

stage in prosecution requires approval from the Technology Center director. Applicant further argues that the seven inventions are classified in the same class/subclass and that one cannot restrict within a single claim.

This is not persuasive because the previous restriction requirement and notice of allowance was filed by a previous Examiner. As a note, restriction practice varies according to the Examiner. Furthermore, it is noted that the new rules did not go into effect as planned, therefore the Applicant's arguments are moot. Although the seven inventions are classified in the same class/subclass, a search for one particular disease will not lead to information regarding another patentably distinct disease in the non patent literature.

Applicants argue against the enablement rejection by claiming that a link exists between p38 and various diseases, highlighted by the Badger reference. Applicants also corroborate their argument by referring to the in vitro raf kinase assays and in vivo assays in the specification, which is allegedly routine the field to correlate inhibition of p38 to therapeutic treatment of various diseases.

This is not persuasive because although there may be link between p38 and various diseases this does not correlate to actually treating a disease in any therapeutic sense. In fact, inhibition of p38 is not well known in the field to be correlated to any particular disease. The Badger reference is an isolated reference that cannot be taken as the standard for the state of art concerning inhibition of p38 and the treatment of various diseases. Furthermore, the enablement rejection also pertains to the fact that

there would be undue experimentation to determine every known disease to be associated with p38.

The specification does not disclose how one of ordinary skill in the art would determine every known disease associated with p38, let alone effectively treat that disease with a p38 inhibitor considering various factors such as side effects, toxicity, and dosing. There is no indication that such a link actually translates to the treatment of the disease. The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass virtually every disease or disorder that is mediated by p38 kinase.

It is noted that the specification also lacks any factual evidence of actual therapeutic treatment of a disease associated with p38. It is not well established in the field to correlate inhibition of p38 to actual treatment of a disease. Moreover, there is no raw data for any of the disclosed compounds in the examples of the specification. The mice are not disclosed to have a p38 mediated disease or disorder, therefore no disease is being treated in the examples.

### ***Conclusion***

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not


mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

YSC

  
SREENI PADMANABHAN  
SUPERVISORY PATENT EXAMINER